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Stereoselective Synthesis of Chiral 2,3-Disubstituted 2,3-Dihydro-4(1*H*)-pyridones

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The alkylation at C-3 of the easily accessible (*R*)-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-1-[(*S*)-1-phenylethyl]-2,3-dihydro-4(1*H*)-pyridone with different electrophiles took place with total *trans* diastereoselectivity to afford the corresponding (2*R*,3*S*)-2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones in enantiomerically pure form. The configuration at C-3 can be inverted by deprotonation and subsequent reprotonation to yield the corresponding (2*R*,3*R*)-2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones in a highly diastereoselective manner.

Introduction

Numerous natural compounds and synthetic derivatives with interesting biological activities[1] and useful chemotherapeutic profiles[2] feature piperidine subunits as an essential pharmacophoric motif. Piperidines with various substitution patterns exhibit different pharmacological properties and, as a consequence, research into the development of synthetic strategies for the preparation of polysubstituted piperidines in enantiomerically pure form has grown dramatically in recent years.[3]

As a part of a programme aimed at the design and preparation of polyfunctionalised, chiral building blocks that are useful for the asymmetric synthesis of biologically active nitrogen-containing compounds, we have studied the behaviour of (*R*)-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-1-[(*S*)-1-phenylethyl]-2,3-dihydro-4(1*H*)-pyridone (**1**) as a synthetic precursor to obtain chiral 2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones in enantiomerically pure form. This synthetic intermediate is easily available on gram scale from inexpensive D-mannitol,[4] which comes from renewable sources. The ease with which C-2 and/or C-4 can be functionalised is well illustrated by the expedient asymmetric synthesis of (*R*)-4-oxopipecolic acid,[5] (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-*N*-*tert*-butyl-4-hydroxypipecolamide,[6] (*R*)- and (*S*)-2-substituted 4-alkylidenepiperidines,[7] (2*R*,4*S*)- and (2*R*,4*R*)-4-phosphonomethylpiperidine-2-carboxylic acids,[8] *cis*- and *trans*-1,2,4-trisubstituted piperidines,[9] (*R*)-quinuclidine-2-carboxylic acid[10] and (2*R*,4*R*)-*N*-(*tert*-butoxycarbonyl)-4-[2-(methoxycarbonylamino)ethyl]pipecolic acid.[11]

In this paper, we detail the functionalisation of 2,3-dihydro-4(1*H*)-pyridone **1** at C-3 with the diastereoselective alkylation of the corresponding enolate as a synthetic strategy. In this context, the methylation at C-3 of the six-membered heterocyclic ring in chiral 2-substituted *N*-(alkoxycarbonyl)-2,3-dihydro-4(1*H*)-pyridones has been successfully exploited by Comins an co-workers as an approach to the asymmetric synthesis of dienomycin C,[12] indolizidine alkaloids,[13] several benzomorphane derivatives[14] and other piperidine-containing compounds.[15] Kunz et al. studied the alkylation of chiral enolates derived from 2-substituted *N*-arabinopyranosyl-2,3-dihydro-4(1*H*)-pyridones with methyl and ethyl iodide,[16] and Ma and co-workers reported the alkylation of a chiral 2-substituted 4-oxoquinoline with 2-bromoethyl trifluoromethanesulfonate in a route to martinellic acid[17]. The alkylation at C-3 of some racemic 2-substituted 2,3-dihydro-4(1*H*)-pyridones directed to the synthesis of azadecalines has also been described.[18] Finally, during the preparation of this manuscript, Wanner and Ege[19] described the diastereoselective methylation and benzylation of racemic 2-substituted *N*-acyl-2,3-dihydro-4(1*H*)-pyridones as a key step in the synthesis of 2,3-disubstituted β-amino acid derivatives.

Results and Discussion

2,3-Dihydro-4(1*H*)-pyridone **1** was obtained by the reaction of Danishefsky's diene with (*S*)-2,3-di-*O*-benzyl-*N*-[(*S*)-1-phenylethyl]glyceraldimine as described previously.[4] The optimization of the reaction of **1** with methyl iodide was first examined by exploring several bases (Table 1). Compound **1** in THF was deprotonated with a slight excess of base (1.1 equiv.) at –78 °C for 30 min. Methyl iodide was then added in excess (4.8 equiv.), and after 3 h at –78 °C, the reaction was quenched with aqueous ammonium chlo-

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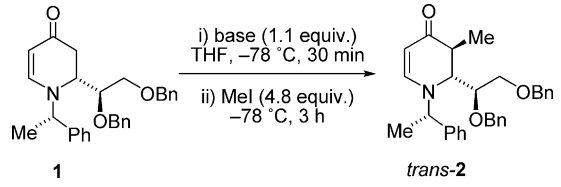
ride. In all cases, the methylated product **2**, with a *trans* configuration, was obtained in diastereomerically pure form, as determined by ^{1}H and ^{13}C NMR analyses.

Table 1. Diastereoselective methylation of **1**.



1 *trans*-**2**

Entry	Base	**2**/**1**[a]	*trans*/*cis*[a]	Yield[b]
1	LDA	95:5	>98:2	64%
2	LiHMDS	95:5	>98:2	66%
3	NaHMDS	>98:2	>98:2	68%
4	KHMDS	77:23	>98:2	52%
5	*n*BuLi	>98:2	>98:2	48%
6	*s*BuLi	81:19	>98:2	39%
7	*t*BuLi	73:27	>98:2	40%

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of the *trans* diastereomer.

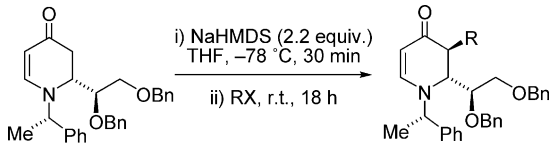
As shown in Table 1, the best results were obtained with NaHMDS. By using this base, the conversion was complete, and **2** was isolated in 68% yield. When LDA or LiHMDS were used, the isolated yield of **2** was similar, but some unreacted starting material was detected in the reaction mixture. The use of other bases such as KHMDS, *n*BuLi, *s*BuLi or *t*BuLi did not have a positive influence, and a significant decrease in isolated yield was observed under the same reaction conditions.

In an effort to improve the reaction yield, a number of additional experiments with NaHMDS as the base were performed. An increase in the temperature after the addition of methyl iodide, even up to room temperature, did not affect the yield or *trans* diastereoselectivity. When the amount of base was doubled, an increase in isolated yield was observed at room temperature. The combination of the base with some additives such as HMPA or a crown ether, which in some cases have led to noticeable increases in reaction yields,[20] did not have a positive influence in this case. The isolated yield was similar when NaHMDS was used in combination with HMPA, but a substantial decrease was observed when NaHMDS was used in combination with 15-crown-5.

The optimal isolated yield of *trans*-**2** (74%) was obtained when the starting compound was treated with 2.2 equiv. of NaHMDS at –78 °C for 30 min. After the addition of 4.8 equiv. of methyl iodide at –78 °C, the reaction mixture was warmed to room temperature, stirred for 18 h, and then quenched with aqueous ammonium chloride.

Having optimised the reaction conditions, the scope and limitations of the alkylation of **1** with a range of electrophiles was investigated. The results are given in Table 2. The reaction of the enolate derived from **1** with ethyl iodide under the same conditions as described above was investigated first. This reaction provided the desired product **3** with total *trans* diastereoselectivity but with a lower isolated yield. In an attempt to increase the yield, the amount of alkylating agent was doubled. It was gratifying to find that in contrast to the results with methyl iodide, doubling the amount of ethyl iodide provided ethylated *trans*-**3** in improved yield.

Table 2. Diastereoselective alkylation of **1**.



1 *trans*-**2**–**8**

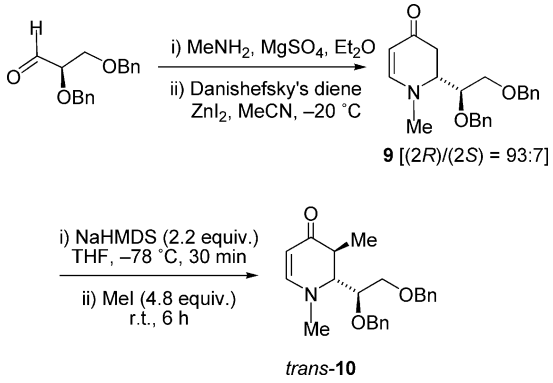
Entry	RX (equiv.)	Product	*dr*[a]	Yield[b]
1	MeI (4.8)	*trans*-**2**	>98:2	74%
2	EtI (4.8)	*trans*-**3**	>98:2	55%
3	MeI (9.6)	*trans*-**2**	>98:2	71%
4	EtI (9.6)	*trans*-**3**	>98:2	66%
5	*n*PrI (9.6)	*trans*-**4**	>98:2	56%
6	*n*BuI (9.6)	*trans*-**5**	>98:2	58%
7	CH_2=$CHCH_2$Br (9.6)	*trans*-**6**	>98:2	59%
8	BnBr (9.6)	*trans*-**7**	>98:2	53%
9	*t*Bu$O_2$$CCH_2$Br (9.6)	*trans*-**8**	>98:2	57%

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of the *trans* diastereomer.

The reaction of **1** with several other alkylating agents showed similar results. Alkyl, allyl and benzyl halides and *tert*-butyl bromoacetate reacted to give satisfactory yields and total *trans* diastereoselectivities regardless of the size of the electrophile.

In order to study the synthesis of *cis*-2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones from *trans*-2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones through a deprotonation/reprotonation sequence, a new substrate was obtained according to Scheme 1. Treatment of 2,3-di-*O*-benzyl-D-glyceraldehyde with methylamine in the presence of anhydrous $MgSO_4$ afforded the corresponding *N*-methylimine. This compound reacted with Danishefsky's diene in the presence of a ZnI_2 catalyst at low temperature in anhydrous CH_3CN to give cyclic enaminone **9** as a diastereomeric mixture (*dr* = 93:7), in which the (2*R*) diastereomer predominated. The methylation of **9** as described above cleanly led to a mixture of compounds with a *trans* configuration, from which *trans*-**10** was isolated in 77% yield.

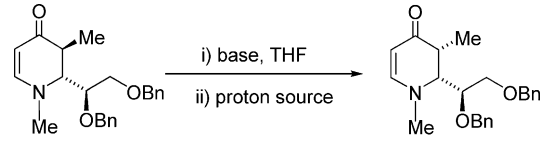
Several bases and reaction conditions were explored for the epimerisation of C-3 in *trans*-**10** (Table 3). Both the extent of the epimerisation and the isolated yield of the *cis* diastereomer depended on the base and the reaction conditions. The epimerisation only occurred to a considerable extent when LDA was used in excess. Otherwise, unreacted *trans*-**10** was recovered, or the *cis* diastereomer was the minor compound in the product mixture. At room temperature, the crude reaction mixture was contaminated with a series of unidentified by-products, a situation that led to poor isolated yields of *cis*-**10**. Lowering the temperature to –78 °C significantly improved the *cis* stereoselectivity and diminished the secondary reactions. The proton source



Scheme 1. Synthesis of *trans*-**10**.

proved to have a significant influence on the extent of epimerisation, and the best results were obtained with aqueous ammonium chloride. The best results overall were obtained by the treatment of *trans*-**10** with an excess of LDA (2.0 equiv.) at –78 °C for 14 h and subsequent neutralisation with aqueous ammonium chloride. Under these conditions, the major product, *cis*-**10**, was isolated in 61% yield.

Table 3. Diastereoselective epimerisation of *trans*-**10**.

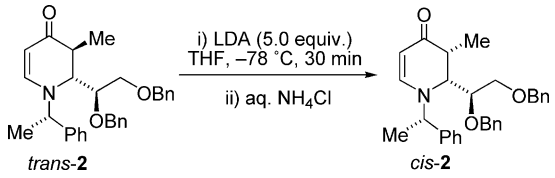


Entry	Base (equiv.)	Proton source	*T* [°C]	*t* [h]	*trans*/*cis*[a]	Yield[b]
1	LDA (1.1)	aq. NH_4Cl	r.t.	18	62:38	18%
2	LDA (2.0)	aq. NH_4Cl	r.t.	18	16:84	32%
3	LiHMDS (2.0)	aq. NH_4Cl	r.t.	12	71:29	13%
4	NaHMDS (2.0)	aq. NH_4Cl	r.t.	72	>98:2	–
5	LDA (2.0)	aq. NH_4Cl	–78	14	9:91	61%
6	LDA (2.0)	MeOH	–78	14	28:72	38%
7	LDA (2.0)	*i*PrOH	–78	14	24:76	51%

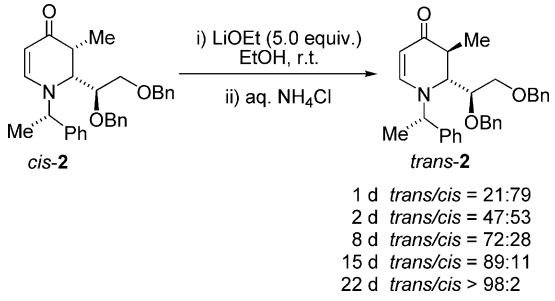
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of the *cis* diastereomer.

The treatment of *trans*-**2** with LDA as described above led to an 84:16 *cis*/*trans* diastereomeric mixture, from which the major compound, *cis*-**2**, was isolated in 57% yield. The yield and diastereoselectivity were better with a large excess of LDA (5.0 equiv.) and after 30 min neutralisation with aqueous ammonium chloride at –78 °C. These new conditions allowed for the isolation of *cis*-**2** in 81% yield from the 94:6 *cis*/*trans* diastereomeric mixture obtained (Scheme 2).

We attempted to identify the thermodynamically most stable diastereomer. Disubstituted 2,3-dihydro-4(1*H*)-pyridones **2** of *cis* and *trans* configuration were treated with several bases such as KOH, KO*t*Bu and LiOEt. Whereas *trans*-**2** was recovered after several days, *cis*-**2** slowly isomerised to *trans*-**2**. The epimerisation of *cis*-**2** with LiOEt, generated in situ by the addition of 5.0 equiv. of LiHMDS to anhydrous ethanol, was monitored by ^{1}H NMR spectroscopy. We observed that the treatment of *cis*-**2** at room temperature with a large excess of LiOEt (5.0 equiv.), followed after 22 d by neutralisation with aqueous ammonium chloride, led to the exclusive formation of *trans*-**2** (Scheme 3). This result clearly indicates that *trans*-**2** is thermodynamically more stable than *cis*-**2**.



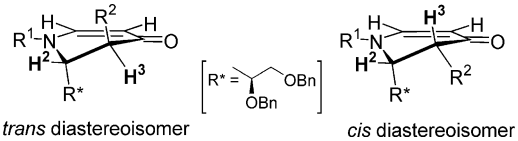
Scheme 2. Epimerisation of *trans*-**2**.



Scheme 3. Thermodynamic epimerisation of *cis*-**2**.

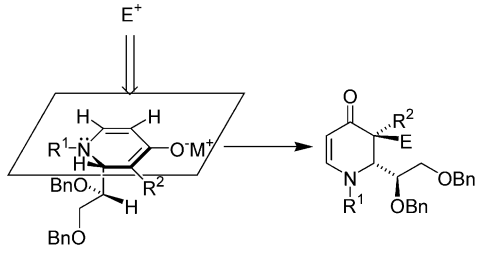
The relative configurations of all the 2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones were unambiguously determined on the basis of their vicinal homonuclear ^{1}H-^{1}H coupling constants (Table 4). Theoretical calculations of $^3J_{2\text{-H},3\text{-H}}$ in 2,3-disubstituted *N*-(alkoxycarbonyl)-2,3-dihydro-4(1*H*)-pyridones revealed[21] that $^{cis}J_{2\text{-H},3\text{-H}} \approx 5$ Hz > $^{trans}J_{2\text{-H},3\text{-H}} \approx 1$ Hz, which is consistent with other results reported in the literature.[19,22] The pseudoaxial disposition adopted by the C-2 substituent in 1,2,3-trisubstituted 2,3-dihydro-4(1*H*)-pyridones to minimise 1,2-allylic strain[23] [$A^{(1,2)}$] accounts for the small value of $^3J_{2\text{-H},3\text{-H}}$ observed in the *trans* diastereoisomers.

Table 4. $^3J_{2\text{-H},3\text{-H}}$ values.



Entry	Compound	R^1	R^2	$^3J_{2\text{-H},3\text{-H}}$
1	*trans*-**2**	(*S*)-CH(Me)Ph	Me	1.3 Hz
2	*cis*-**2**	(*S*)-CH(Me)Ph	Me	6.3 Hz
3	*trans*-**3**	(*S*)-CH(Me)Ph	Et	1.3 Hz
4	*trans*-**4**	(*S*)-CH(Me)Ph	*n*Pr	1.4 Hz
5	*trans*-**5**	(*S*)-CH(Me)Ph	*n*Bu	1.3 Hz
6	*trans*-**6**	(*S*)-CH(Me)Ph	$CH_2CH{=}CH_2$	1.2 Hz
7	*trans*-**7**	(*S*)-CH(Me)Ph	Bn	0 Hz
8	*trans*-**8**	(*S*)-CH(Me)Ph	CH_2CO_2tBu	0 Hz
9	*trans*-**10**	Me	Me	1.3 Hz
10	*cis*-**10**	Me	Me	6.8 Hz

The total diastereoselectivity of the alkylation fully agrees with other results previously reported in the literature and can be rationalised by taking into account the structural properties of the enolate acting as the nucleophile. As a consequence of the strong sp^2-hybridised character of the nitrogen atom in the enaminone system, the intermediate endocyclic enolate must be almost planar, with the nitrogen substituent placed in the heterocycle plane. This forces the bulky substituent at C-2 into a pseudoaxial orientation to minimise 1,2-allylic strain.[23] In this situation, the attack of the electrophile opposite to the C-2 substituent leading to *trans* compounds will be favoured on the basis of both steric and stereoelectronic arguments (Figure 1). The same rationale would explain the formation of *cis* compounds in the protonation of enolates derived from *trans*-**2** or *trans*-**10**.



Alkylation

M = Li, Na, K; R^1 = Me, (*S*)-CH(Me)Ph; R^2 = H;
E = Me, Et, *n*Pr, *n*Bu, $CH_2CH{=}CH_2$, Bn, CH_2CO_2tBu

Protonation

M = Li; R^1 = Me, (*S*)-CH(Me)Ph; R^2 = Me; E = H

Figure 1. Stereochemical course of enolate neutralisation.

Conclusions

(*R*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-1-[(*S*)-1-phenylethyl]-2,3-dihydro-4(1*H*)-pyridone (**1**) is a versatile synthetic intermediate for the asymmetric synthesis of 2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones by alkylation at C-3 as the key step. Reaction of **1** with alkyl, allyl and benzyl halides and *tert*-butyl bromoacetate allowed for the preparation of *trans*-2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones with the (2*R*,3*S*) configuration in enantiomerically pure form. Once the *trans* diastereomer with a (2*R*,3*S*) configuration was obtained, we converted it into the corresponding *cis* diastereomer with a (2*R*,3*R*) configuration by deprotonation with an appropriate base and subsequent reprotonation. We note that this synthetic strategy allows the synthesis of 2,3-disubstituted 2,3-dihydro-4(1*H*)-pyridones that are structurally and stereochemically diverse at C-3 with a simple methodology.

Experimental Section

General: All reagents were of analytical grade and were used as obtained from commercial sources. Reactions were carried out with anhydrous solvents. Whenever possible, the reactions were monitored by thin layer chromatography (TLC). TLC was performed with precoated silica gel polyester plates, and products were visualised with UV light (254 nm) and exposed to ethanolic phosphomolybdic acid solution, followed by heating. Column chromatography was performed with silica gel (Kiesegel 60, 230–400 mesh). Melting points were determined in open capillaries with a Gallenkamp capillary melting point apparatus and are not corrected. IR spectra of oils were recorded as thin films with NaCl plates with a Thermo Nicolet Avatar 360 FT-IR spectrometer; $\tilde{\nu}$ values expressed in cm^{-1} are given for the main absorption bands. NMR spectra were acquired with Bruker AV spectrometers operating at 500 or 400 MHz for ^1H NMR and 125, 100 or 75 MHz for ^{13}C NMR at room temperature in $CDCl_3$ with a 5 mm probe. Chemical shifts (δ) are reported in parts per million (ppm) and were referenced to the residual solvent peak. Coupling constants (J) are quoted in Hz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; m, multiplet; br. s, broad singlet; br. d, broad doublet; dd, doublet of doublets; qd, quartet of doublets; ddd, doublet of doublet of doublets; qdd, quartet of doublet of doublets; br. dd, broad doublet of doublets; dddd, doublet of doublet of doublet of doublets. Optical rotations were measured with a Jasco 1020 polarimeter at λ = 589 nm and 25 °C in a cell with 10 cm path length; $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm g^{-1}, and concentrations are given in g/100 mL. High-resolution mass spectra were recorded with a Bruker Daltonics MicroToF-Q electrospray instrument from methanolic solutions with the positive electrospray ionization mode (ESI^+). (*R*)-2,3-Di-*O*-benzylglyceraldehyde[24] and (*R*)-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-1-[(*S*)-1-phenylethyl]-4-piperidone[4] (**1**) were prepared as described previously in the literature.

General Procedure for the Diastereoselective Alkylation of (*R*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-1-[(*S*)-1-phenylethyl]-2,3-dihydro-4(1*H*)-pyridone (1): A solution of (*R*)-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-1-[(*S*)-1-phenylethyl]-2,3-dihydro-4(1*H*)-pyridone (**1**, 221 mg, 0.5 mmol) in anhydrous THF (10 mL) was added to NaHDMS (1.0 M in THF, 1.10 mL, 1.1 mmol), diluted in anhydrous THF (5 mL) at –78 °C under argon, and the mixture was stirred at –78 °C for 30 min. The appropriate alkylating agent (2.4 or 4.8 mmol) was then added at –78 °C, and the reaction mixture was warmed to room temperature. After stirring at room temperature for 18 h, saturated aqueous NH_4Cl (15 mL) was added carefully with stirring. The mixture was extracted with Et_2O (3 × 20 mL), the combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. Purification of the residue by filtration through a silica gel path gave the corresponding (2*R*,3*S*)-2,3-disubstituted-2,3-dihydro-4(1*H*)-pyridone.

(2*R*,3*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-2,3-dihydro-3-methyl-1-[(*S*)-1-phenylethyl]-4(1*H*)-pyridone (*trans*-2): The residue was purified by filtration through a silica gel path (eluent: AcOEt) to afford *trans*-**2** (168 mg, 74%). Oil. $[\alpha]_D^{25}$ = –20.1 (*c* = 1.29, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1634, 1576 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 7.3 Hz, 3 H), 1.59 (d, *J* = 6.9 Hz, 3 H), 2.36 (qdd, *J* = 7.3, 1.3, 1.2 Hz, 1 H), 3.56 (dd, *J* = 11.2, 3.9 Hz, 1 H), 3.75 (ddd, *J* = 8.2, 1.4, 1.3 Hz, 1 H), 3.78 (dd, *J* = 11.2, 2.4 Hz, 1 H), 4.03 (ddd, *J* = 8.2, 3.9, 2.4 Hz, 1 H), 4.51 (d, *J* = 11.7 Hz, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 4.57 (d, *J* = 12.1 Hz, 1 H), 4.70 (dd, *J* = 7.5, 1.2 Hz, 1 H), 4.71 (d, *J* = 11.7 Hz, 1 H), 4.74 (q, *J* = 6.9 Hz, 1 H), 6.67 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.22–7.41 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 19.8, 40.3, 62.2, 62.7, 67.7, 72.2, 73.3, 76.9, 94.6, 127.6, 127.7, 127.7, 127.8, 128.2, 128.2, 128.3 (2 C), 128.7, 137.8, 138.0, 139.0, 148.6, 195.0 ppm. HRMS: calcd. for $C_{30}H_{34}NO_3$ $[M + H]^+$ 456.2533; found 456.2527.

(2*R*,3*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-3-ethyl-2,3-dihydro-1-[(*S*)-1-phenylethyl]-4(1*H*)-pyridone (*trans*-3): The residue was purified by fil-

tration through a silica gel path (eluent: AcOEt/hexanes, 3:1) to afford *trans*-**3** (155 mg, 66%). Oil. $[\alpha]_D^{25}$ = –9.2 (*c* = 0.93, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1633, 1585 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (dd, *J* = 7.4, 7.4 Hz, 3 H), 1.29–1.44 (m, 1 H), 1.47 (d, *J* = 6.9 Hz, 3 H), 1.50–1.65 (m, 1 H), 2.00 (dddd, *J* = 8.0, 7.0, 1.3, 1.2 Hz, 1 H), 3.46 (dd, *J* = 11.2, 3.8 Hz, 1 H), 3.66 (dd, *J* = 11.2, 2.2 Hz, 1 H), 3.80 (ddd, *J* = 8.2, 1.3, 1.3 Hz, 1 H), 3.94 (ddd, *J* = 8.2, 3.8, 2.2 Hz, 1 H), 4.41 (d, *J* = 11.7 Hz, 1 H), 4.43 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 4.60 (d, *J* = 11.7 Hz, 1 H), 4.60 (dd, *J* = 7.4, 1.2 Hz, 1 H), 4.64 (q, *J* = 6.9 Hz, 1 H), 6.58 (dd, *J* = 7.4, 1.3 Hz, 1 H), 7.11–7.31 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 19.9, 25.0, 47.6, 60.2, 62.3, 67.6, 72.1, 73.4, 76.9, 95.0, 127.7 (2 C), 127.7, 127.8, 128.2, 128.2, 128.4 (2 C), 128.7, 137.8, 138.0, 139.2, 148.6, 194.3 ppm. HRMS: calcd. for $C_{31}H_{35}NO_3Na$ $[M + Na]^+$ 492.2635; found 492.2633.

(2*R*,3*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-2,3-dihydro-1-[(*S*)-1-phenylethyl]-3-*n*-propyl-4(1*H*)-pyridone (*trans*-4): The residue was purified by filtration through a silica gel path (eluent: AcOEt/hexanes, 2:1) to afford *trans*-**4** (135 mg, 56%). Oil. $[\alpha]_D^{25}$ = –8.4 (*c* = 0.59, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1631, 1582 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (dd, *J* = 7.0, 7.0 Hz, 3 H), 1.18–1.43 (m, 3 H), 1.42–151 (m, 1 H), 1.48 (d, *J* = 6.9 Hz, 3 H), 2.12 (br. dd, *J* = 6.9, 6.9 Hz, 1 H), 3.46 (dd, *J* = 11.2, 3.8 Hz, 1 H), 3.66 (dd, *J* = 11.2, 2.2 Hz, 1 H), 3.79 (ddd, *J* = 8.2, 1.4, 1.3 Hz, 1 H), 3.94 (ddd, *J* = 8.2, 3.8, 2.2 Hz, 1 H), 4.41 (d, *J* = 11.8 Hz, 1 H), 4.43 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 4.60 (d, *J* = 11.8 Hz, 1 H), 4.61 (dd, *J* = 7.4, 1.1 Hz, 1 H), 4.64 (q, *J* = 6.9 Hz, 1 H), 6.59 (dd, *J* = 7.4, 1.3 Hz, 1 H), 7.11–7.35 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 19.9, 20.1, 33.9, 45.6, 60.3, 62.4, 67.7, 72.2, 73.5, 77.0, 95.1, 127.7, 127.7, 127.7, 127.8, 128.2, 128.3, 128.4, 128.4, 128.8, 137.9, 138.1, 139.2, 148.7, 194.5 ppm. HRMS: calcd. for $C_{32}H_{37}NO_3Na$ $[M + Na]^+$ 506.2666; found 506.2684.

(2*R*,3*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-3-*n*-butyl-2,3-dihydro-1-[(*S*)-1-phenylethyl]-4(1*H*)-pyridone (*trans*-5): The residue was purified by filtration through a silica gel path (eluent: AcOEt/hexanes, 2:1) to afford *trans*-**5** (144 mg, 58%). Oil. $[\alpha]_D^{25}$ = –13.8 (*c* = 0.57, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1628, 1589 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (dd, *J* = 7.0, 7.0 Hz, 3 H), 1.26–1.43 (m, 4 H), 1.38–1.49 (m, 1 H), 1.54–1.65 (m, 1 H), 1.58 (d, *J* = 6.9 Hz, 3 H), 2.19 (dddd, *J* = 7.4, 7.4, 1.3, 1.2 Hz, 1 H), 3.57 (dd, *J* = 11.2, 3.8 Hz, 1 H), 3.77 (dd, *J* = 11.2, 2.2 Hz, 1 H), 3.89 (ddd, *J* = 8.2, 1.3, 1.3 Hz, 1 H), 4.04 (ddd, *J* = 8.2, 3.8, 2.2 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.53 (d, *J* = 12.1 Hz, 1 H), 4.57 (d, *J* = 12.1 Hz, 1 H), 4.70 (d, *J* = 11.7 Hz, 1 H), 4.70 (dd, *J* = 7.4, 1.2 Hz, 1 H), 4.74 (q, *J* = 6.9 Hz, 1 H), 6.70 (dd, *J* = 7.4, 1.3 Hz, 1 H), 7.21–7.27 (m, 2 H), 7.26–7.40 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 20.0, 22.6, 29.2, 31.5, 45.9, 60.3, 62.4, 67.8, 72.2, 73.5, 77.0, 95.2, 127.7, 127.7, 127.7, 127.8, 128.2, 128.2, 128.4, 128.4, 128.8, 137.9, 138.1, 139.3, 148.7, 194.5 ppm. HRMS: calcd. for $C_{33}H_{40}NO_3$ $[M + H]^+$ 498.3003; found 498.3009.

(2*R*,3*S*)-3-Allyl-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-2,3-dihydro-1-[(*S*)-1-phenylethyl]-4(1*H*)-pyridone (*trans*-6): The residue was purified by filtration through a silica gel path (eluent: AcOEt/hexanes, 2:1) to afford *trans*-**6** (142 mg, 59%). Oil. $[\alpha]_D^{25}$ = –53.7 (*c* = 0.81, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1640, 1631, 1589 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 6.9 Hz, 3 H), 2.16–2.25 (m, 1 H), 2.37–2.44 (m, 1 H), 2.40–2.48 (m, 1 H), 3.58 (dd, *J* = 11.1, 4.3 Hz, 1 H), 3.76 (dd, *J* = 11.1, 2.4 Hz, 1 H), 3.93 (ddd, *J* = 7.7, 1.2, 1.2 Hz, 1 H), 4.04 (ddd, *J* = 7.7, 4.3, 2.4 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.57 (d, *J* = 12.0 Hz, 1 H), 4.69 (q, *J* = 6.9 Hz, 1 H), 4.70 (d, *J* = 11.7 Hz, 1 H), 4.75 (dd, *J* = 7.5, 0.9 Hz, 1 H), 5.12–5.18 (m, 2 H), 5.74–5.84 (m, 1 H), 6.74 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.22–7.29 (m, 2 H), 7.29–7.42 (m, 13 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3, 35.8, 45.4, 59.6, 62.3, 68.1, 72.2, 73.4, 77.1, 95.3, 117.3, 127.7, 127.7, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 128.8, 135.6, 137.9, 138.0, 139.4, 149.0, 193.3 ppm. HRMS: calcd. for $C_{32}H_{36}NO_3$ $[M + H]^+$ 482.2690; found 482.2683.

(2*R*,3*S*)-3-Benzyl-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-2,3-dihydro-1-[(*S*)-1-phenylethyl]-4(1*H*)-pyridone (*trans*-7): The residue was purified by filtration through a silica gel path (eluent: AcOEt/hexanes, 2:1) to afford *trans*-**7** (141 mg, 53%). Oil. $[\alpha]_D^{25}$ = –65.8 (*c* = 1.26, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1636, 1588 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.9 Hz, 3 H), 2.55 (dd, *J* = 14.3, 11.3 Hz, 1 H), 2.76 (dd, *J* = 11.3, 4.2 Hz, 1 H), 3.02 (dd, *J* = 14.3, 4.2 Hz, 1 H), 3.46 (dd, *J* = 11.0, 5.1 Hz, 1 H), 3.61 (dd, *J* = 11.0, 2.4 Hz, 1 H), 3.62 (br. d, *J* = 7.0 Hz, 1 H), 3.84 (ddd, *J* = 7.0, 5.1, 2.4 Hz, 1 H), 4.25 (d, *J* = 11.8 Hz, 1 H), 4.31 (d, *J* = 11.9 Hz, 1 H), 4.39 (q, *J* = 6.9 Hz, 1 H), 4.42 (d, *J* = 11.9 Hz, 1 H), 4.43 (d, *J* = 11.8 Hz, 1 H), 4.74 (d, *J* = 7.5 Hz, 1 H), 6.72 (dd, *J* = 7.5, 0.7 Hz, 1 H), 7.02–7.30 (m, 20 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 37.6, 46.2, 59.3, 62.2, 68.7, 72.1, 73.4, 77.3, 95.7, 126.5, 127.6, 127.6, 127.6, 127.8, 127.8, 128.3, 128.3, 128.3, 128.5, 128.9, 129.1, 137.9, 138.0, 138.2, 139.8, 149.3, 193.3 ppm. HRMS: calcd. for $C_{36}H_{38}NO_3$ $[M + H]^+$ 532.2846; found 532. 2861.

(2*R*,3*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-3-[(*tert*-butoxycarbonyl)-methyl]-2,3-dihydro-1-[(*S*)-1-phenylethyl]-4(1*H*)-pyridone (*trans*-8): The residue was purified by filtration through a silica gel path (eluent: AcOEt/hexanes, 2:1) to afford *trans*-**8** (158 mg, 57%). Oil. $[\alpha]_D^{25}$ = +5.6 (*c* = 1.09, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1727, 1638, 1580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H), 1.52 (d, *J* = 6.9 Hz, 3 H), 2.29 (dd, *J* = 15.5, 11.7 Hz, 1 H), 2.45 (dd, *J* = 15.5, 3.4 Hz, 1 H), 2.64 (dd, *J* = 11.7, 3.4 Hz, 1 H), 3.53 (dd, *J* = 11.0, 3.1 Hz, 1 H), 3.69 (dd, *J* = 11.0, 1.8 Hz, 1 H), 3.96–4.03 (m, 2 H), 4.42 (d, *J* = 11.4 Hz, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 4.62 (q, *J* = 6.9 Hz, 1 H), 4.62 (d, *J* = 11.4 Hz, 1 H), 4.64 (d, *J* = 7.5 Hz, 1 H), 6.61 (d, *J* = 7.5 Hz, 1 H), 7.10–7.34 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 28.0, 36.3, 43.0, 59.4, 62.4, 68.7, 72.4, 73.5, 76.2, 80.9, 95.6, 127.5, 127.7, 127.7, 128.0, 128.2, 128.3, 128.3, 128.3, 128.8, 138.0, 138.0, 139.4, 149.5, 170.5, 191.8 ppm. HRMS: calcd. for $C_{35}H_{41}NO_5Na$ $[M + Na]^+$ 578.2877; found 578.2891.

(2*R*,3*R*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-2,3-dihydro-3-methyl-1-[(*S*)-1-phenylethyl]-4(1*H*)-pyridone (*cis*-2): A solution of (2*R*,3*R*)-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-2,3-dihydro-3-methyl-1-[(*S*)-1-phenylethyl]-4(1*H*)-pyridone (*trans*-**2**, 228 mg, 0.5 mmol) in anhydrous THF (10 mL) was added to LDA (2.0 M solution in *n*-heptane/THF/ethylbenzene, 1.25 mL, 2.5 mmol), diluted in anhydrous THF (5 mL) at –78 °C under argon, and the mixture was stirred at –78 °C for 30 min. The reaction mixture was then warmed to room temperature, and saturated aqueous NH_4Cl (15 mL) was added carefully with stirring. The mixture was extracted with Et_2O (3 × 20 mL), the combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were evaporated in vacuo to yield **2** as a 94:6 mixture of *cis*/*trans* diastereoisomers. Purification of the residue by silica gel column chromatography (eluent: AcOEt/hexanes, 2:1) gave *cis*-**2** (184 mg, 81%) as an oil. $[\alpha]_D^{25}$ = +27.4 (*c* = 0.95, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1646, 1589 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 7.3 Hz, 3 H), 1.56 (d, *J* = 6.8 Hz, 3 H), 2.92 (qd, *J* = 7.3, 6.3 Hz, 1 H), 3.55 (dd, *J* = 10.4, 5.6 Hz, 1 H), 3.76 (dd, *J* = 10.4, 4.3 Hz, 1 H), 3.82 (ddd, *J* = 6.3, 5.8, 1.0 Hz, 1 H), 3.92 (ddd, *J* = 5.8, 5.6, 4.3 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.51 (q, *J* = 6.8 Hz, 1 H), 4.51 (d, *J* = 11.4 Hz, 1 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.63 (d, *J* = 11.4 Hz, 1 H), 4.82 (d, *J* = 7.4 Hz, 1 H), 6.71 (dd, *J* = 7.4, 1.0 Hz, 1 H), 7.20–7.38 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 20.1,

41.7, 60.5, 61.7, 70.3, 73.2, 73.4, 76.5, 97.6, 127.6, 127.7, 127.7, 127.9, 128.0, 128.0, 128.3, 128.4, 128.7, 137.9, 138.1, 139.5, 150.0, 193.7 ppm. HRMS: calcd. for $C_{30}H_{34}NO_3$ $[M + H]^+$ 456.2533; found 456. 2544.

(*R*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-2,3-dihydro-1-methyl-4(1*H*)-pyridone (9): To a solution of crude (*R*)-2,3-di-*O*-benzylglyceraldehyde (456 mg, 1.69 mmol) in anhydrous Et_2O (10 mL) were added successively anhydrous $MgSO_4$ (305 mg, 2.54 mmol) and methylamine (2.0 M in THF, 0.85 mL, 1.69 mmol). After stirring at room temperature for 6 h, the reaction mixture was filtered and concentrated in vacuo to afford the crude imine, which was dissolved in anhydrous CH_3CN (5 mL), added to ZnI_2 (98% suspension, 574 mg, 1.8 mmol) in anhydrous CH_3CN (20 mL), and cooled under argon at –20 °C. The mixture was stirred at –20 °C for 10 min, Danishefsky's diene (0.47 mL, 2.5 mmol) was added, and stirring was continued at –20 °C for 16 h. The mixture was treated with saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The residue obtained was purified by column chromatography (1st eluent: Et_2O/hexanes, 4:1; 2nd eluent: AcOEt) to afford 356 mg (60%) of 2,3-dihydro-4(1*H*)-pyridone **9** as a 93:7 mixture of (2*R*)/(2*S*) diastereoisomers. Data for the (2*R*) diastereomer: IR (neat): $\tilde{\nu}$ = 1635, 1592 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.27 (ddd, *J* = 16.9, 1.5, 1.2 Hz, 1 H), 2.83 (dd, *J* = 16.9, 7.2 Hz, 1 H), 3.18 (s, 3 H), 3.52 (dd, *J* = 11.1, 3.6 Hz, 1 H), 3.71 (dd, *J* = 11.1, 2.6 Hz, 1 H), 3.77 (dddd, *J* = 8.7, 7.2, 1.5, 1.1 Hz, 1 H), 4.11 (ddd, *J* = 8.7, 3.6, 2.6 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.55 (s, 2 H), 4.66 (d, *J* = 11.7 Hz, 1 H), 4.81 (dd, *J* = 7.3, 1.2 Hz, 1 H), 6.81 (dd, *J* = 7.3, 1.1 Hz, 1 H), 7.27–7.40 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.8, 44.3, 59.0, 68.0, 72.4, 73.5, 75.8, 96.3, 127.7, 127.8, 127.8, 128.1, 128.4, 128.4, 137.7, 137.7, 153.1, 189.7 ppm. HRMS: calcd. for $C_{22}H_{25}NO_3Na$ $[M + Na]^+$ 374.1727; found 374. 1742.

(2*R*,3*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-2,3-dihydro-1,3-dimethyl-4(1*H*)-pyridone (*trans*-10): A solution of a 93:7 mixture of (*R*)-/(*S*)-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-2,3-dihydro-1-methyl-4(1*H*)-pyridone (**9**, 176 mg, 0.5 mmol) in anhydrous THF (10 mL) was added to NaHDMS (1.0 M solution in THF, 1.10 mL, 1.1 mmol), diluted in anhydrous THF (5 mL) at –78 °C under argon, and the mixture was stirred at –78 °C for 30 min. Methyl iodide (0.15 mL, 2.4 mmol) was then added at –78 °C, and the reaction mixture was warmed to room temperature. After the mixture had been stirred at room temperature for 6 h, saturated aqueous NH_4Cl (15 mL) was added carefully with stirring. The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The residue obtained was purified by filtration through a silica gel path (eluent: AcOEt) to afford 141 mg (77%) of *trans*-**10** as an oil. $[\alpha]_D^{25}$ = –172.3 (*c* = 0.64, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1634, 1592 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 7.3 Hz, 3 H), 2.16 (qdd, *J* = 7.2, 1.3, 0.9 Hz, 1 H), 3.18 (s, 3 H), 3.42 (ddd, *J* = 9.0, 1.3, 1.2 Hz, 1 H), 3.48 (dd, *J* = 11.1, 3.5 Hz, 1 H), 3.67 (dd, *J* = 11.1, 2.5 Hz, 1 H), 3.99 (ddd, *J* = 9.0, 3.5, 2.5 Hz, 1 H), 4.41 (d, *J* = 11.7 Hz, 1 H), 4.49 (d, *J* = 12.2 Hz, 1 H), 4.54 (d, *J* = 12.2 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.69 (dd, *J* = 7.2, 0.9 Hz, 1 H), 6.74 (dd; *J* = 7.2, 1.2 Hz, 1 H), 7.22–7.37 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 40.6, 45.1, 65.0, 67.8, 72.4, 73.3, 75.8, 94.0, 127.6, 127.7, 127.8, 128.1, 128.3, 128.3, 137.7, 137.7, 151.8, 194.5 ppm. HRMS: calcd. for $C_{23}H_{28}NO_3$ $[M + H]^+$ 366.2064; found 366. 2058.

(2*R*,3*R*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-2,3-dihydro-1,3-dimethyl-4(1*H*)-pyridone (*cis*-10): A solution of (2*R*,3*R*)-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-2,3-dihydro-1,3-dimethyl-4(1*H*)-pyridone (*trans*-**10**, 183 mg, 0.5 mmol) in anhydrous THF (10 mL) was added to LDA (2.0 M solution in *n*-heptane/THF/ethylbenzene, 0.50 mL, 1.0 mmol), diluted in anhydrous THF (5 mL) at –78 °C under argon, and the mixture was stirred at –78 °C for 14 h. The reaction mixture was then warmed to room temperature, and saturated aqueous NH_4Cl (15 mL) was added carefully with stirring. The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were evaporated in vacuo to yield **10** as a 91:9 mixture of *cis*/*trans* diastereoisomers. Purification of the residue by silica gel column chromatography (1st eluent: Et_2O; 2nd eluent: AcOEt) gave *cis*-**10** (111 mg, 61%) as an oil. $[\alpha]_D^{25}$ = –97.5 (*c* = 0.83, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1642, 1596 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 7.2 Hz, 3 H), 2.16 (qd, *J* = 7.2, 6.8 Hz, 1 H), 3.07 (s, 3 H), 3.55 (dd, *J* = 10.3, 5.3 Hz, 1 H), 3.59 (dd, *J* = 6.8, 5.6 Hz, 1 H), 3.66 (dd, *J* = 10.3, 4.8 Hz, 1 H), 3.91 (ddd, *J* = 5.6, 5.3, 4.8 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.54 (d, *J* = 11.9 Hz, 1 H), 4.60 (d, *J* = 11.4 Hz, 1 H), 4.85 (d, *J* = 7.2 Hz, 1 H), 6.86 (d, *J* = 7.2 Hz, 1 H), 7.23–7.39 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 40.9, 43.3, 63.0, 70.1, 73.0, 73.4, 76.0, 96.7, 126.6, 126.7, 127.8, 127.8, 128.3, 128.4, 137.7, 138.0, 153.6, 193.6 ppm. HRMS: calcd. for $C_{23}H_{28}NO_3$ $[M + H]^+$ 366.2064; found 366.2061.

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